REMARKS

Claims 79-84, 86-89, and 92-94 stand rejected in the present Office Action. No claims have been amended or cancelled in the present response. As such, Claims 79-84, 86-89, and 92-94 are currently pending.

I. The Claims are Enabled and Supported by Adequate Written Description

The Examiner rejected Claims 82 and 94 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the invention was filed, had possession of the claimed invention (Office Action pages 2-3). Applicants respectfully disagree. The Examiner alleges that support for a dosage of 15 mg/kg/day, as provided in the Specification, for example, in table 6, described administration to rabbits, not to humans as claimed. However, an animal model, as provided in the specification, constitutes a working example if it correlates with the claimed invention. *MPEP* §2164.02. The examples must reasonably correlate (*In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995)), but an invariable exact correlation is not required. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). Applicants respectfully assert that"[t]he rabbit endocarditis model is now very well standardized and is accepted as a rigorous test of the ability of antimicrobial agents to cure severe human infections" (See Specification, page 23, lines 22-24; and See, e.g., Carbon, C. (1993) Experimental endocarditis: a review of its relevance to human endocarditis. *Journal of Antimicrobial Chemotherapy* 31, *Suppl. D*, 71–85. Abstract, Appendix A; Zak, O. & O'Reilly, T. (1991). Animal models in the evaluation of antimicrobial agents. *Antimicrobial Agents and Chemotherapy* 35, 1527–31, Appendix B; and Fantin, B. & Carbon, C. (1992). *In vivo* antibiotic synergism: contribution of animal models. *Antimicrobial Agents and Chemotherapy* 36, 907–12, Appendix C). Accordingly, Applicants respectfully assert that the model used correlates with the claimed use in humans, and the Specification reasonably conveys to one of ordinary skill in the art that the inventors at the time the application was filed had possession of the claimed invention. Applicants respectfully request that the Examiner withdraw each rejection made under 35 U.S.C. §112, first paragraph.

II. The Claims are Not Obvious

The Examiner rejected Claims 79-84, 86-89, and 92-94 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Zygmunt, Goldberg and Stark, and further in view of Oldham. Applicants respectfully disagree.

The Examiner alleges that Zygmut teaches lysostaphin dosages in the range of 0.5 to 50 mg/kg, or multiple doses in the range of 0.5 to 50 mg/kg (Office Action, page 4). The Examiner further alleges that it would have been obvious to select the claimed dosage of 3-25 mg/kg because it is a result-effective variable, within the range taught by Zygmut, which may be optimized by an artisan in the course of routine optimization (Office Action, page 4). Applicants respectfully disagree with the Examiner's allegation that the claimed dosage is a result-effective variable.

Specifically, Applicants assert that the claimed dosage had not been recognized by the art to attain or provide a recognizably beneficial result. Furthermore, the claimed range provides unexpected benefits not achieved or suggested by the cited references and the cited references teach away from the claimed dosage of the invention.

A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie,* 559 F.2d 618, 621 (CCPA 1977); *In re Boesch,* 617 F.2d 272, 276 (CCPA 1980)("[D]iscovery of an optimum value of a result effective variable … is ordinarily within the skill of the art."); *see also In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.").

Thus, Aller stands for the principle that the discovery of an optimum value of a variable in a known process is normally obvious. *In re Antonie*, 559 F.2d 618, 620, 195 USPQ 6, 8-9 (CCPA 1977). Exceptions to this general rule lie in cases where the results of optimizing a variable, which was known to be result effective, were unexpectedly good or where the parameter optimized was not recognized to be a result-effective variable. Id.

Applicants respectfully assert that experiments conducted during development of embodiments of the invention permitted Applicants to recognize a method of treating a subject with a staphylococcal infection of an organ with a dose of 3-25 mg/kg/day of the type claimed to be a result-effective variable bearing on the ability to result in a 3 fold or greater reduction in Staphylococcus burden. There is nothing in Zygmut, considered alone or in any combination with Goldberg, Stark or Oldham, which demonstrates that this recognition was shared by the prior art. In other words, the applied references do not establish that a dose of lysostaphin of 3-25 mg/kg/day to a human subject harboring a staphylococcal infection of an organ was an art-recognized result-effective variable. Applicants respectfully assert that this fact situation falls into one of the exceptions to the general rule established by Aller, and for this reason, the claims are not obvious.

Moreover, Applicants respectfully assert that the administration of dosages within the claimed range (e.g., to dogs 7 and 10 in Goldberg) of the prior art did not effectively treat infection of organs in subjects and also lead to relapse in the subjects. Moreover, one of ordinary skill in the art would have had to proceed contrary to the teachings of Goldberg to arrive at the claimed invention. Thus, in order to arrive at the claimed invention, one of ordinary skill in the art would have had to employ dosages in humans which had been disclosed in Goldberg as resulting in eventual relapse and high levels of resistant strains in dogs.

Accordingly, Applicants respectfully assert that the cited references direct one of ordinary skill in the art away from the claimed invention. In particular, one of ordinary skill in the art would understand Goldberg, and Zygmunt summarizing the same, to teach the use of higher doses (e.g., 50 mg/kg/day or more) that provide results that were not achievable with lower dosages of the claimed invention. Goldberg did not suggest the utility of a method of treating a staphylococcal infection of an organ in a human subject, comprising: providing a subject comprising a staphylococcal infection, wherein the infection comprises infection of an organ; and administering to the subject a recombinantly produced lysostaphin in a dose of 3-25 mg/kg/day, wherein the administering results in a 3-fold or greater reduction of staphylococci present in the subject. In fact, Goldberg teaches the avoidance of methods of treatment of the claimed invention. In particular, the ordinarily skilled person would have been motivated to select a dosage regimen for lysostaphin that is characterized by high dose (e.g., at least 50

mg/kg), and not a dose of the claimed invention (e.g., as recited in Claims 79, 94, and claims dependent thereon).

According to the MPEP, a *prima facie* case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. *In re Geisler*, 116F.3d 1465, 1471, 43 USPQ3d 1362, 1366 (Fed. Cir. 1997). MPEP §2144.05(III). Moreover, a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (See MPEP §2141.02). Rebuttal evidence may also include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art. Rebuttal evidence may consist of a showing that the claimed compound possesses unexpected properties. *Dillon*, 919 F.2d at 692-93, 16 USPQ2d at 1901. A showing of unexpected results must be based on evidence, not argument or speculation. *In re Mayne*, 104 F.3d 1339, 1343-44, 41 USPQ2d 1451, 1455-56 (Fed. Cir. 1997).

Although Applicants do not believe a *prima facie* case of obviousness has been established, a *prima facie* case of obviousness based on overlapping ranges can be rebutted by showing the criticality of the claimed range. "The law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims. . . . In such a situation, the applicant must show that the particular range is critical, generally by showing that the claimed range achieves **unexpected results** relative to the prior art range." *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).

Any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really **unexpected**. *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Unexpected results for a claimed range as compared with the range disclosed in the prior art have been shown by a demonstration of a marked improvement over the art, as to be classified as **a difference in kind, rather than one of degree**." *In re Waymouth*, 499 F.2d 1273, 1276, 182 USPQ 290, 293 (CCPA 1974).

Goldbergh teaches that administration of dosages between 3-25 mg/kg/day **did not** achieve the same result as administration of higher doses (e.g., 50 mg/kg/day). Specifically, dogs administered lower dosages in the claimed range displayed an increase in lysostaphin resistant strains and also relapse, two highly unfavorable outcomes.

> "The largest proportions of isolates found to be resistant were in three dogs receiving small repeated doses. The emergence of resistant isolates in these dogs may have resulted from repeated exposure to small amounts of enzyme. These three dogs relapsed, perhaps as a result of the large proportion of resistant staphylococci, or perhaps because the small doses of enzyme were insufficient to control the infection." (Goldberg, page 52, left column, beginning at second full paragraph).

The claims recite treating a methicillin-resistant staphylococcal infection of an organ by administering lysostaphin in a dose of 3-25 mg/kg/day. Experiments performed during development of embodiments of the invention demonstrate the effectiveness of such treatment:

> "As shown in table 6, a regimen of 5mg/kg lysostaphin three times daily was the most efficacious treatment. An impressive statistic is that this treatment completely sterilizied the heart valve vegetation in all but one of the rabbits. This was far superior to the standard regimen used as a positive control in this infection model: 30 mg/kg vancomycin twice daily. A regimen of 5 mg/kg lysostaphin once daily was less efficacious than the thrice daily regimen, but was almost as good as vancomycin in reducing bacterial counts in the vegetation; in fact, the effect was not statistically different from the vancomycin group." (Specification, page 20, lines 18-28, see also Table 6).

Results achieved by the claimed invention stand in stark contrast to the teaching of Goldbergh that dosages between 3-25 mg/kg/day did not achieve the same result as administration of higher doses, resulted in the emergence of resistant isolates, and were insufficient to control infection. The results achieved by the claimed treatment represent a "difference in kind," rather than one of degree, and are therefore unexpected results for the claimed range as compared with the range disclosed by Goldbergh. *In re Waymouth*, 499 F.2d 1273, 1276, 182 USPQ 290, 293 (CCPA 1974). The claimed treatment provides unexpected results and therefore rebuts the *prima facie* case of obviousness alleged by the Examiner.

Previous work with lysostaphin in established organ infections showed limited reduction of bacterial load in a kidney mouse model, and in heart valves and other organs in a dog endocarditis model, at doses ranging from 50 to 250 mg/kg/treatment (Specification, paragraphs 0008-0010). Despite the significantly higher dosages used in these studies, effectiveness of the magnitude required in the treatment of organ infections was not observed. The results obtained previously would not have led to the prediction of the rapid, total sterilization of virtually all

heart valve vegetations, as was demonstrated using the very moderate doses of lysostaphin of the claimed invention. The claimed methods provide heretofore unachieved and unexpected results and therefore rebut the *prima facie* case of obviousness alleged by the Examiner.

The Examiner has failed to establish a *prima facie* case of obviousness

Applicants respectfully submit that Zygmunt and Goldberg not only fail to teach or suggest a method of treating an established organ infection in a human subject via administering to the subject lysostaphin in a dose of 3-25 mg/kg/day, the teachings of Zygmunt and Goldberg actually teach away from the claimed methods. Stark and Oldham do not overcome this deficiency. In particular, Goldberg specifically teaches that lower dosages (e.g., in the claimed range) lead to the formation of lysostaphin resistant strains. Specifically, dogs 7, and 10 exemplify why one of ordinary skill in the art would be lead away from the claimed invention. Table 4 shows that dogs 7, and 10 displayed 83 and 66 %, respectively, lysostaphin resistant strains in the blood, and dog 7 displayed 94 % lysostaphin resistant strains in tissue.

Table 1 of Goldberg indicates that dogs 7 and 10 had significant levels of staphylococci in both blood and heart valve cultures. Moreover, according to Table 1 of Goldberg, dog 7 had 3,775 colonies/ml and dog 10, which was not tested for bacteria in heart valve cultures, had 280 colonies/ml of staphylococci in blood cultures prior to autopsy. In contrast, dogs in the "well dogs" category had no more than 5 colonies/ml in blood cultures prior to autopsy. Similarly, in heart valve cultures, dog 7 had 10^8 colonies/g in both aortic and mitral valve cultures whereas the dogs in the "well dogs" category had no more than 102 colonies/g in aortic valve cultures and no more than 103 colonies/g in mitral valve cultures. Moreover, according to Goldberg: [d]espite initial improvement, five dogs relapsed (relapsed dogs) 1.5 to 2.2 days after the first dose of lysostaphin. Although additional lysostaphin was administered after the relapse occurred in dogs 8 and 10, no effect on the course of the infection was apparent, and dog 10 subsequently expired. (page 48 of Goldberg). The relapsed dogs are designated as Dogs 6-10 in Table I of Goldberg. Accordingly, Goldberg clearly discloses that the dogs in the "Relapsed Dogs" category, which includes Dogs 7 and 10, had a negative outcome. In fact, Dog 10 expired even though additional lysostaphin was administered after relapse occurred.

Accordingly, Applicants respectfully assert that a *prima facie* showing of obviousness has not been made with respect to the amended claims.

Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness. To the extent the Examiner has established such a case, Applicants assert that the *prima facie* case of obviousness is rebutted by unexpected results of the claimed invention, and by a showing that the art teaches away from the claimed invention. Accordingly, Applicants respectfully request that the rejection of the Claims under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that Applicants have addressed all grounds for rejection and Applicants' claims should be passed to allowance. Reconsideration of the application is respectfully requested. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (608) 662-1277.

Respectfully submitted,

Date: 01 March 2010

/Tyler J. Sisk/
Tyler J. Sisk
Registration No. 59,850

CASIMIR JONES, S.C.
2275 Deming Way, Suite 310
Middleton, Wisconsin 53562
608.662.1277